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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,088	01/14/2008	Manzer Durrani	20695C-006210US	6451

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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
12/01/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipefiling@kilpatricktownsend.com
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Office Action Summary	Application No.	Applicant(s)	
	10/579,088	DURRANI ET AL.	
	Examiner	Art Unit	
	CLAIRE KAUFMAN	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *72-77* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *72-77* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/6/11 has been entered.

The Office regrets the delay in responding.

The rejections under 35 USC 112, first and second paragraphs, are moot in view of the cancelation of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 72-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,618,786 (IDS filed 1/14/08) and US 6,267,958 (PTO-892 mailed 8/27/09) in view of US 6,653,284 (PTO-892 mailed 7/6/10), US 5,166,134 (IDS filed 1/14/08), and US 6,991,824 B2 (cited here).

US 5,618,786 teaches an aerosol formulation in which recombinant AAT (col. 4, lines 16-17) is in an amount to provide 1μg to 10mg/kg of host or 0.1-15 weight % of formulation, though "the amount employed will vary depending upon a number of factors, including the size

of the particle, frequency of administration, nature of the disease, whether the treatment is for therapeutic or prophylactic purposes, etc." (col. 3, lines 5-7 and 25-31). Also included may be lactose (col. 3, line 10 and 16-17) and a surfactant (*e.g.*, a diglyceride; col. 3, lines 10-18). The AAT is used "to inhibit elastase, a proteolytic enzyme affecting lung tissue and implicated as a major cause of emphysema" (col. 2, lines 21-24). The AAT may be purified or recombinant (*e.g.*, claim 9). US 5,618,786 does not teach the glycosylation state of the AAT, or the inclusion of an antioxidant in the formulation. Concentrations of 0.01-0.5% w/v of surfactant and 1-5% w/v of carbohydrate are not explicitly taught.

US 6,267,958 teaches a generally applicable pharmaceutical composition comprising a protein, exemplified by HER-2 antibody, but which may be AAT, wherein the composition may be lyophilized or aqueous and the protein is at a concentration in aqueous formulation at about 5-50 mg/ml (col. 6, lines 49, and col. 17, lines 5-15). Included in the composition may be a carbohydrate, called a "lyoprotectant", such as trehalose (col. 9, lines 21-25), a surfactant such as polysorbate 80 present at about 0.001-0.5% (col. 15, lines 36-59) and an antioxidant such as methionine (col. 16, lines 5-9). The lypoprotectant enables the protein to essentially retain its physical and chemical stability and integrity upon lyophylization and storage (col. 9, lines 36-38). The composition is also taught reconstituted with a diluent, which includes water (*e.g.,* col. 2, lines 20-23). The effects of trehalose concentration from 60mM to 200mM on stability of lyophilized HER2 antibody at 40°C are show in FIG. 2. FIG. 3 shows that over a 200 day period, 250mM trehalose provided superior stability compared to 60mM trehalose. Aggregation of the antibody was assayed wherein the lyoprotectant was mannitol, lactose, maltose, trehalose or sucrose at 40°C for up to 52 weeks as shown in FIG. 12. Trehalose (solid squares) was significantly better than any other lyoprotectant. The same was true at 2-8°C (FIG. 11). It is noted that (col. 17, lines 55-61), "The appropriate dosage ("therapeutically effective amount") of the protein will depend, for example, on the condition to be treated, the severity and course of the condition, whether the protein is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the protein, the type of protein used, and the discretion of the attending physician." Further (col. 10, lines 12-17), "The protein to be formulated is prepared using techniques which are well established in the art including synthetic

techniques (such as recombinant techniques and peptide synthesis or a combination of these techniques) or may be isolated from an endogenous source of the protein."

US 6,653,284 teaches a pharmaceutical formulation for keratinocyte growth factor-2 (KGF-2) which comprises an antioxidant such as methionine at about 0.1-2% w/v ([[59] and claim 69) or ascorbic acid at about 0.01-2% w/v, a surfactant such as polysorbate 80 at about 0.003-0.02% ([59]), and a carbohydrate such as sucrose or trehalose at about 0.01-5% w/v (claims 41 and 57).

US 5,166,134 teaches AAT in an aqueous pharmaceutical formulation wherein the AAT is 0.1 to 4.5% by weight of the solution (col. 2, lines 58-61) and is in combination with an antioxidant such as vitamin E and a carbohydrate such as sorbitol (col. 4, lines 22-27 and Example 2). The solution may be 10% saline (Example 1). The AAT may be in a glycosylated or nonglycosylated recombinant form (col. 3, lines 17-19). AAT is reported to be especially useful because of its association with elastase and kinins (col. 3, lines 36-37). It is stated that (col. 3, lines 44-46), "The recombinant gene product of the invention is especially useful since it is free of contaminating viruses when produced." "Serine protease inhibitors such as α_1-antitrypsin and α_1-antichymotrypsin have been found to be useful in the treatment of dermatitis by inhibition and/or binding with elastase, cathepsin G and human mast cell chymase." (col. 1, lines 57-61) Application by inhalation to the lung is taught (*e.g.*, col. 4, lines 43-51).

US 6,991,824 teach detection of recombinant human AAT from engineered plants as a means to produce human milk proteins recombinantly for addition to foods or infant formulas (col. 25, lines 1-6). PBS is known as phosphate buffered saline and was usually used for protein extraction as a 10 mM solution at 7.4 (col. 68, lines 36-40). Western Blotting and ELISA assay for AAT were performed using washes with pH 7.4 PBS (col. 55, lines 8-42). PBS was also used to test thermo and pH stability of AAT (col. 59, line 55, to col. 60, line 63).

It would have been obvious at the time the invention was made to one of ordinary skill in the art to have a pharmaceutical preparation of AAT as a powder, as taught for aerosolization by US 5,618,786 or for lyophilization for storage by US 6,267,958, or aqueous form as taught by US 5,166,134. AAT was known to inhibit elastase (see US 5,618,786 and US 5,166,134) and be present in human milk (US 6,991,824) and have therapeutic benefits. As stated in US 5,618,786, the AAT may be purified (native) or recombinant. The amount of AAT present depends on

many factors including route and frequency of administration, nature of disease, use as therapeutic or prophylactic, etc., as discussed by US 5,618,786 and US 6,267,958. Further, the recombinant AAT may be from engineered plant and present in 10mM sodium phosphate buffer (PBS) at pH 7.4 as taught by US 6,991,824. It would have been obvious and desirable to include a carbohydrate/lyoprotectant such as trehalose, antioxidant such as methionine and surfactant for their old and well known stabilization and lung and tissue penetration properties, respectively. It would have been desirable to use trehalose as compared to other carbohydrates such as lactose because US 6,267,958 showed that trehalose was better than several other carbohydrates (including lactose) at inhibiting protein aggregation and was highly effective in maintaining protein stability over a wide range of temperatures and pH's. It further would have been routine optimization to determine favorable formulation concentrations of the different components based on the guidance in the pharmaceutical prior art, such as a surfactant in the range of 0.001-0.5% w/v (*e.g.,* US 6,267,958), an antioxidant in the range of 0.1-2% w/v (*e.g.,* US 6,653,284), carbohydrate in the range of 0.01-5% w/v (*e.g.,* US 6,653,284) and AAT in the range of 1-10 mg/kg or 0.1-15% w/v (*e.g.,* US 5,618,786). It further would have been obvious to use recombinant AAT because US 5,166,134 states it would be free of contaminating viruses and can be produced in a number of different cell types including plant cells (*e.g.,* US 6,991,824). Similarly, whether the AAT is glycosylated or not (see, *e.g.*, US 5,166,134) would reasonably be expected to depend on its source and desirability of using either type since it was old and well known how to obtain glycosylated or unglycosylated proteins.

Applicants argue that the instantly claimed invention is particularly effective in maintaining stability of AAT at a variety of temperatures and that this ability is a surprising and unexpected result (see Tables 1 and 2 of the specification). Of the nine formulations tested, those in which trehalose was present at at least 2.5% had the most beneficial effects on stability. The argument has been fully considered, but is not persuasive. The specification shows that when AAT activity was tested at 60°C, formulas F2, F4 and F9, all of which had less than 2.5% trehalose had lower activity than those formulas with at least 2.5% trehalose. However, F1, which had no trehalose or surfactant, showed comparable AAT activity to F7, which had 2.5%

trehalose (see Table 2B). It is obvious from the table there is significant variability in measurements for most formulations (*e.g.*, F1 at month 1 is 51.5, at 2 is 71.2 and at 3 months is 51.4). Therefore, one skilled in the art cannot definitively say that trehalose had an unexpected effect on activity. The specification also shows the result of storage under different conditions on monomer concentration (Table 3B). It was found that protein concentration or Tween-80 did not affect monomer concentration. It is stated (p. 18, lines 25-27) that when trehalose was varied, "The first available change occurs at 40°C storage temperatures, with the most dramatic effects at 60°C (Table 3B)." Nevertheless, this finding is not surprising or unexpected in view of the known effects of trehalose on protein stability and particularly monomer concentration as detailed in US 6,267,958. One skilled in the art must also question the relevancy of data for storage at a temperature as high as 60°C (140°F). The combination of elements know in the prior art yielded predictable results, with no change in the respective functions of the elements. For the reasons which include the variability in AAT activity data in the specification, the lack of effect on stability of components of the claimed composition other than trehalose, and the knowledge in the prior art that trehalose is highly effective in promoting protein stability, the rejection is maintained as applied to the new claims.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Kaushik et al. (J. Biol. Chem. 278(29), 26458026465, 18 July 2003) reaffirms that trehalose is an exceptional protein stabilizer and shows for different temperatures and pH's for a number of proteins (*e.g.*, Fig. 1). As stated at the beginning of the "DISCUSSION" section on p. 26462, "*Exceptional Stabilization by Trehalose*—Among the various osmolytes selected by nature to counteract deleterious environmental effects, trehalose seems to be exceptional among the compatible osmolytes of the sugar and the polyol series, because
it increases the transition temperature (ΔTm) of proteins to a maximal extent."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire Kaufman, whose telephone number is (571) 272-0873. She can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire Kaufman
/Claire Kaufman/
Patent Examiner, Art Unit 1646
November 18, 2011